UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/823,356	03/30/2001	Y. Tom Tang	PF-0489-1 CON	9453

22428 7590 06/09/2004

FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
MURPHY, JOSEPH F	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

Mailed 6-9-04

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 05062004

Application Number: 09/823,356
Filing Date: March 30, 2001
Appellant(s): TANG ET AL.

Shirley A. Recipon
Cathleen M. Rocco
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 3/2/2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences that will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

As to Issue 1

Appellant's Brief contains a statement that the claims stand or fall together.

As to Issue 2

Appellant's Brief contains a statement that the claims stand or fall together.

As to Issue 3

Appellant's Brief contains a statement that the claims stand or fall together.

As to Issue 4

Appellant's Brief contains a statement that the claims stand or fall together.

As to Issue 5

Appellant's brief includes a statement that this issue pertains only to claim 7.

As to Issue 6

Appellant's brief includes a statement that this issue pertains only to claims 3, 5-7, 9, 11-12, 79 and 80.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Doerks et al. Protein annotation: detective work for function prediction. Trends in Genetics. June 1998, Vol. 14, No. 6, pages 248-250.

Bork et al. Go Hunting in sequence databases but watch out for the traps. Trends in Genetics 1996, 12:425-427

Brenner et al. Errors in Genome Annotation. Trends in Genetics 1999, 15:132-133

Voet et al. Biochemistry. 1990. John Wiley & Sons, Inc. pages 126-128 and 228-234

Rockett et al., Differential gene expression in drug metabolism and toxicology: Practicalitiess problems and potential, Xenobiotica 29(7):655 (1999).

Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, Proceedings of the National Academy of Sciences USA 94:8945 (Aug. 1997).

Emile F. Nuwaysir et al., Microarrays and toxicology: The advent of toxicogenomics, Molecular Carcinogenesis 24:153 (1999).

Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology - potentials and limitations, Toxicology Letters 112-113:467 (2000).

John C. Rockett and David J. Dix, Application of DNA arrays to toxicologv, Environmental Health Perspectives 10748):681 (1999).

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC §§ 101, 112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 5-7, 9, 11-12, 79-80, 83 are rejected, under 35 U.S.C. § 101 because they are drawn to an invention with no apparent or disclosed patentable utility. The instant application has provided a description of an isolated DNA encoding a protein and the protein encoded thereby, for reasons of record set forth in Paper NO. 10, 2002. The instant application does not disclose the biological role of this protein or its significance. The claimed invention is not

supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well-established utility and must undergo extensive experimentation. Appellant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

It is clear from the instant specification that the nucleic acid encoding the MSP-9 polypeptide has been assigned a function because of its similarity to known proteins (Specification at 30, line 4). However, it is commonly known in the art that sequence-to-function methods of assigning protein function are prone to errors (Doerks et al.1998). These errors can be due to sequence similarity of the query region to a region of the alleged similar protein that is not the active site, as well as homologs that did not have the same catalytic activity because active site residues of the characterized family were not conserved (Doerks et al. page 248, column 3, fourth and fifth paragraphs). Inaccurate use of sequence-to-function methods have led to significant function-annotation errors in the sequence databases (Doerks et al. page 250, column 1, third paragraph). Furthermore, Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

After complete characterization, this protein may be found to have a patentable utility. This further characterization, however, is part of the act of invention and until it has been undertaken Appellant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson,* 148 USPQ 689 (Sup. Ct., 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 USC § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an Appellant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

The instant claims are drawn to a nucleic acid encoding a polypeptide that has an as yet undetermined function or biological significance. Until some actual and specific significance can be attributed to the protein identified in the specification as MSP-9, the instant invention is incomplete. The polypeptide encoded by the nucleic acids of the instant invention is alleged to be structurally analogous to a protein that is known in the art as the IL-1 receptor intracellular domain ligand. In the absence of knowledge of the biological significance of this protein, there

is no immediately obvious patentable use for it. To employ a protein of the instant invention in the identification of substances that inhibit its activity is clearly to use it as the object of further research that has been determined by the courts to be a non-patentable utility. Since the instant specification does not disclose a "real world" use for MSP-9 then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 USC § 101 as being useful.

Claims 3, 5-7, 9, 11-12, 79-80, 83 are rejected, under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Even if, *arguendo*, the nucleic acid of the instant invention is found to have a patentable utility, claims 3-7, 9, 11-12, 79-80, 83 are rejected, under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid encoding an amino acid of SEQ ID NO: 9, or a nucleic acid with the sequence as set forth in SEQ ID NO: 26, does not reasonably provide enablement for a nucleic acid which encodes a naturally occurring amino acid sequence 90% identical to SEQ ID NO: 26, for reason of record set forth in Paper No. 10, 9/26/2002. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 3, 5-7, 9, 11-12, 79-80, 83 are overly broad since insufficient guidance is provided as to which of the myriad of variant nucleic acids encode polypeptides which will retain the characteristics of MSP-9. Appellants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible variants of MSP-9. It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein

can have dramatic effects on the protein's function. It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

Since the claims encompass variant nucleic acids and polypeptides and given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to make and use the claimed invention. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The claims as written do not set forth a functional limitation for the polynucleotides encoding polypeptides encompassed by the claims. The claims recite that the polynucleotide encodes a naturally occurring polypeptide 90% identical to SEQ ID NO: 9. The Specification only sets forth the amino acid sequence of SEQ ID NO: 9. It would require undue experimentation for one of skill in the art to make the claimed polynucleotides because the skilled artisan would need to isolate polynucleotides from natural sources, then determine which encode polypeptides at least 90% identical to SEQ ID NO: 9. However, since there is no functional limitation set forth for the encoded polypeptide, and the function of MSP-9 is not known, it would require undue experimentation for the skilled artisan to make polynucleotides encoding naturally occurring amino acid sequences 90% identical to SEQ

ID NO: 9 since the skilled artisan would be required to determine the function of the encoded polypeptide. The amino acid sequence of a polypeptide determines its structural and functional properties, and the predictability of which amino acids can be substituted is extremely complex and outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the polynucleotide and the encoded polypeptides are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Appellant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass polynucleotides and encoded polypeptides which the specification only teaches one skilled in the art to test for functional variants. It would require undue experimentation for one of skill in the art to make and use the claimed polynucleotides and encoded polypeptides, since the skilled artisan would have to first make polynucleotides encoding polypeptide variants, but there is no functional limitation set forth for the encoded polypeptides. Thus, since Appellant has only taught how to test for polynucleotide and polypeptide variants of MSP-9, and has not taught how to make polynucleotide and polypeptide variants of MSP-9, it would require undue experimentation of one of skill in the art to make and use the claimed polynucleotide.

Claims 3, 5-7, 9, 11-12, 79-80, 83 are rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record set forth in

paper NO. 10, 9/26, 2002. Appellant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

These are genus claims. The claims are drawn to a nucleic acid which encodes a naturally occurring amino acid sequence which is 90% identical to SEQ ID NO: 9. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to the encoded SEQ ID NO: 26. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, a nucleic acid with a sequence as set forth in SEQ ID NO: 9, and the polypeptide of SEQ ID NO: 26 is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Appellant was not in possession of the claimed genus.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a host cell in culture comprising a polynucleotide with the sequence as set forth in SEQ ID NO: 26, does not reasonably provide enablement for in vivo transfection, for reasons of record set forth in Paper No. 10, 9/26/2002.

The specification discloses that the nucleic acids of the current invention can be expressed in a wide variety of host cell types, including animal cell systems (Specification at 40, line 15-21) and in vivo (Specification at 52, lines 26-30). However, there are no actual or prophetic examples that disclose how to make or use host cells that comprise a DNA sequence as set forth in SEQ ID NO: 26 in an animal. The Examiner cites Eck & Wilson (page 81, column 2, second paragraph to page 82, column 1, second paragraph) who report that numerous factors complicate *in vivo* gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. Since the instant disclosure does not address any of the methods necessary to make a host cell in an animal that comprises the polynucleotide of interest, the claim as written is not enabled.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Appellant regards as his invention.

Claims 3, 5-7, 9, 11-12, 79-80 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellant regards as the invention, for reasons of record set forth in Paper No. 10, 9/26/2002.

Claims 3, 11 and 12 are indefinite in the recitation of the term "naturally occurring". It is unclear whether this term imposes a required limitation on the claim, such that it only encompasses, for example, polynucleotides amplified from human cDNA, or only sequences produced by digestion with restriction enzymes of DNA isolated from tissue that contains polynucleotides encoding the polypeptide, or if the claim encompasses all polynucleotide sequences that encode the polypeptide. Therefore, the metes and bounds of the claim are unclear. Claims 4-9, 79-80 are rejected due to their dependence on claims 3, 11 and 12.

(11) Response to Argument

Issue 1: It is alleged that the claims meet the utility requirement under 35 USC § 101.

At p. 5, first paragraph of the Brief, Appellant characterizes the invention as a polynucleotide sequence corresponding to a gene that is expressed in human tissues and that codes for a polypeptide that is a member of the class of membrane spanning protein family. Based on this, Appellant urges that the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development and diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the claimed polynucleotide actually functions.

Appellant states that the claimed invention already enjoys significant commercial success. This has been fully considered but is not found to be persuasive for several reasons. The specification does not disclose that the claimed genes are markers for specific diseases. Absent a disclosure of altered levels or forms of a gene in diseased tissue as compared with the corresponding healthy tissue, the gene is not a disease marker or an appropriate target for drug discovery or toxicology testing. Finally, evidence of commercial success, while sometimes persuasive as secondary evidence of non-obviousness, is immaterial to utility and enablement. Many products have enjoyed commercial success due to fads or clever advertising, wherein the products would not have met the legal standards for utility and enablement.

Beginning at p. 6, first paragraph, Appellant discusses the Bedilion declaration submitted with the Brief under 37 CFR 1.132. Appellant characterizes the Bedilion declaration as describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications, thus allegedly demonstrating the examiner's position to be without merit. In particular, Appellant states that the Bedilion declaration describes how the claimed expressed polynucleotide can be used in gene expression monitoring systems that were well-known at the time of the invention, and how those applications are useful in developing drugs and monitoring their activity. Appellant quotes from the Bedilion declaration, that states that microarrays containing SEQ ID NO: 26, encoding SEQ ID NO: 9, would be a more useful tool than microarrays lacking same in connection with conducting gene expression monitoring studies on proposed or actual drugs for treating cell proliferative and developmental disorders for such purposes as evaluating their efficacy and toxicity. This is not found to be persuasive. As an aside, it is noted that Dr. Bedilion is a consultant for Incyte Pharmaceuticals, Inc., the real party

in interest in this appeal, and thus is a concerned party. Regarding the merit of the argument, any new polynucleotide can be used in a microarray, and thus this asserted utility is not specific. Also, the disclosure that MSP-9 is structurally related to membrane spanning proteins does render the asserted utility specific, since the specification does not establish that MSP-9 is expressed in any diseased tissues in any way that is different from the way it is expressed in healthy forms of the same tissues. In other words, the specification does not disclose that MSP-9 is expressed in tissues having cell proliferative or developmental disorders at altered levels or forms. Thus, it is not a target for drug development, toxicology studies, or disease diagnosis. Significant further research would have to be conducted to identify disease states that correlate with altered levels or forms of the claimed polynucleotides. Therefore, this asserted utility is also not substantial.

Beginning at the bottom of p. 6 of the Brief, Appellant criticizes the examiner's position that the claimed polynucleotide cannot be useful without precise knowledge of its biological function. However, Appellant is mischaracterizing the examiner's position. A specification can meet the legal requirements of utility and enablement for a new polynucleotide as long as the specification discloses a credible, specific and substantial asserted utility for the new polynucleotide, or a well-established utility for the claimed polynucleotide. A hypothetical example may serve to clarify. For example, a hypothetical specification discloses that a claimed polynucleotide is expressed in colon cancer and not expressed in healthy colon tissue. The hypothetical specification does not disclose the biological activity of the polypeptide encoded by the polynucleotide. The claimed polynucleotide in the hypothetical example would not be rejected under 35 U.S.C. §§ 101 and 112, first paragraph, as it has utility and is enabled as a

colon cancer marker. However, such is not the fact pattern here. The instant specification discloses that the claimed polynucleotides are structurally related to membrane spanning proteins and hypothesizes that the claimed polynucleotides are involved in cancer, immunological and reproductive disorders, but the expression of the polynucleotide in diseased tissues and the corresponding healthy tissues was not evaluated. Therefore, there is no disclosure that the claimed polynucleotides are expressed at altered levels or forms in any specific, diseased tissue. It is noted that the instant application has an effective filing date of 3/13/1998. No evidence has been brought forth during the prosecution history regarding the expression levels in diseased or healthy tissue. Also, no evidence has been brought forth that the claimed polynucleotides encode polypeptides having specific growth factor activities.

I. The applicable legal standard

Beginning at p. 7 of the Brief, Appellants summarize case law on the utility requirement. The essential disagreement appears to be the interpretation of what constitutes a specific, substantial and credible utility, as will be explained more fully below.

II. Toxicology testing, drug discovery, and disease diagnosis are alleged to be sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

A. The use of MSP-9 for toxicology testing, drug discovery, and disease diagnosis are alleged as practical uses that confer specific benefits to the public:

Appellants argue at pages 8-15 of the Brief that the use of MSP-9 for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer specific benefits to the public. Appellant states that there is no dispute that the claimed invention is a useful tool in

cDNA microarrays used to perform gene expression analysis. Appellant asserts that such is sufficient to establish utility for the claimed polynucleotide. This is not found to be persuasive. While the examiner agrees that any polynucleotide, including the claimed polynucleotides, can be used in a cDNA microarray, such does not confer patentable utility on the claimed polynucleotides. Since any polynucleotide can be used in a microarray, such a use is not specific to the claimed polynucleotides. Just as any orphan receptor can be used in an assay to screen for ligands, such does not confer patentable utility on a particular orphan receptor. Such can be done with any orphan receptor, and thus the asserted utility is not specific. Furthermore, since the specification does not disclose a correlation between any disease or disorder and an altered level or form of the claimed polynucleotides, the results of gene expression monitoring assays would be meaningless without significant further research. Therefore, the asserted utility is also not substantial.

Appellant refers to the Bedilion declaration as explaining the many reasons why a person skilled in the art reading the instant application would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, such as a probe for expression of the polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs. The Bedilion declaration discusses microarrays and Northern analysis for measuring such. Specifically, Appellant quotes from the Bedilion declaration that a person skilled in the art would have been able to use the claimed polynucleotide in gene expression monitoring to develop new drugs for the treatment of cell proliferative and developmental. This is not found to be persuasive. The instant specification does not substantiate a link between the claimed polynucleotides and any specific

cell proliferative or developmental disorder. The specification merely discloses that the claimed polynucleotides are structurally related to growth factors, and that they are expected to be involved in cell proliferative and developmental processes (and thus, disorders). The specification does not disclose the results of the required control in order to draw any conclusions regarding disease, namely, that the claimed polynucleotide is not expressed (or is expressed at an altered level or form) in the corresponding healthy tissues. Many genes expressed in diseased tissues have nothing whatsoever to do with the disease and are not targets for drug development or toxicology. For example, actin and histone genes are expressed in diseased tissues; they are constitutively expressed in all tissues. These are not suitable targets for drug development or toxicology studies, since disruption of these genes would kill the patient.

Beginning at the last paragraph of p. 9 of the Brief, Appellant refers to the opinion of Dr. Bedilion that a person skilled in the art at the time of the invention would have concluded that a cDNA microarray containing the claimed polynucleotide would be a more useful tool than a microarray lacking the claimed polynucleotide in connection with conducting gene expression monitoring studies on proposed or actual drugs for treating cell proliferative or developmental disorders for such purposes as evaluating the efficacy and toxicity. Again, this is not found to be persuasive, because the instant specification has not established that the claimed polynucleotides are expressed at altered levels or forms in diseased tissue as compared with the corresponding healthy tissue. If the claimed polynucleotide were in a microarray and a compound caused decreased expression of the claimed polynucleotide, what would that mean to the skilled artisan? Is it a potential drug, or would administering the compound be likely to acerbate the disease? If it had been disclosed that the claimed polynucleotide is expressed at a higher level in a particular

cell proliferative diseased tissue as compared with the corresponding healthy tissue, then the skilled artisan would know that a compound that decreased expression of the polynucleotide is a good potential cell proliferative disease drug. However, that is not disclosed by the instant specification. The claimed polynucleotides may very well be expressed at equivalent levels in healthy tissues. If that were the case, then the compound would not be a good potential drug. The claimed polynucleotides may also very well be expressed at a lower level in a particular cell proliferative diseased tissue as compared to the corresponding healthy tissue. Then a compound that decreased expression of the claimed polynucleotides would *not* be a good potential drug. Evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

At page 10, Appellant discusses the Bedilion declaration's detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations. Appellant points to Dr. Bedilion's pages of text and numerous subparts explaining the importance of this technology. Appellant points to Dr. Bedilion's explanation that those skilled in the art at the time of the invention without any doubt would have appreciated the criticality of toxicity testing. This is not found to be persuasive. There is no doubt that cDNA microarray technology is an

extremely valuable technique in gene expression monitoring, toxicology testing, and drug efficacy testing. However, the claims are not drawn to the technique. The claims are directed to polynucleotides that have not been disclosed as being associated with any particular disease or condition by its being expressed at an altered level or form in diseased tissue as compared to the corresponding healthy tissue. Any such polynucleotide could be added to a microarray. Thus, this asserted utility is not specific. Determining the relationship between the claimed polynucleotides and any specific disease or disorder would require significant further research. Therefore, this asserted utility is also not substantial.

Appellant urges that the Bedilion declaration establishes that persons skilled in the art, guided by the instant specification, at the time of the invention would have wanted their cDNA microarrays to comprise the claimed polynucleotide, because a microarray comprising the claimed polynucleotide would provide more useful results in the kind of gene expression monitoring studies that microarrays lacking the claimed polynucleotide. This is not found to be persuasive. The specification has not linked the claimed polynucleotide with any specific disease state or disorder, as discussed above and in previous Office Actions. Adding the claimed polynucleotide to a microarray would not make the microarray any more valuable than adding any other "orphan" polynucleotide. The asserted utility is not specific to the claimed polynucleotide.

At the bottom of p. 11 of the Brief, Appellant argues that the examiner does not address the fact that, as described on p. 30 of the specification, the claimed polynucleotide can be used as highly specific probes to measure both the existence and amount of complementary mRNA sequences known to be expression products of the claimed polynucleotides. Appellant concludes

that the claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine. This is not found to be persuasive. Any polynucleotide is a highly specific probe for itself or its complement, or any mRNA that can be transcribed from it. Such can be said for any polynucleotide. Thus, this asserted utility is not specific.

At page 11 of the brief, Appellant argues that, given that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. Appellant reviews case law pertinent to the patentable utility of research tools. This is not found to be persuasive. Appellant's analogy is misplaced. It is true that a scale has patentable utility as a research tool. However, the object being weighed on the scale does not necessarily have patentable utility. In the instant case, microarray technology has patentable utility. However, the microarray is not being claimed, but rather a polynucleotide that can be used in microarrays. The claimed polynucleotide is not disclosed as being expressed at an altered level or form in any diseased tissue as compared to the corresponding healthy tissue. Therefore, the assertion that the claimed polynucleotide has patentable utility as a probe in, or member of, a microarray is not specific. Any orphan polynucleotide can be used in the same way.

At page 11 of the Brief, Appellant argues that there can be no reasonable dispute that persons skilled in the art have numerous uses for information about relative gene expression including understanding the effects of a potential drug for treating cell proliferative and developmental disorders. Appellant urges that, since the specification discloses the claimed polynucleotide to be expressed in cancer and immortalized cell lines, and the fact that the

claimed polynucleotide is structurally related to other growth factors known to be associated with cell proliferative and developmental diseases, the skilled artisan would have derived more information about a potential cell proliferative and developmental disorder drug candidate or potential toxin with the claimed invention than without it. Again, this is not found to be persuasive, because the specification does not disclose that the claimed polynucleotide is expressed at an altered level or form in any particular disease or disorder as compared to the corresponding healthy tissues. It may be useful to consider how broad the term "cell proliferative disorders or developmental disorders" is. Cell proliferative disorders include cancers, psoriasis, warts and slow-closing wounds. Developmental disorders can affect any tissue at any time in its development. Even if it could be assumed that the claimed polynucleotides play a role in a cell proliferative or developmental disorder, determining which disorders are involved and how the claimed polynucleotides are altered during the disorder requires significant further research.

At page 12 of the Brief, Appellant refers to Dr. Bedilion's discussion of the Brown et al. Patent (U.S. 5807522), attached to the declaration. Dr. Bedilion characterizes the patent as providing evidence that microarrays can be used in numerous genetic applications, including monitoring of gene expression in different tissue types, disease states, in response to drugs, and in response to potential toxins. This is not found to be persuasive. The Brown patent claims methods of forming microarrays. Microarray methods have patentable utility as a research tool, just like a scale or a gas chromatograph. However, what the research tool measures does not necessarily have patentable utility, such as the object being weighed by the scale, or the compound being analyzed by the gas chromatograph. Such is the situation at issue.

Appellant refers to other publications that discuss microarrays and gene expression technology with respect to drug screening and toxicology testing at pp. 13-14 of the Brief. Again, this is not found to be persuasive, because the arguments and evidence merely show that microarray technology is important and useful to the scientific community. These publications do not show that the claimed invention has a patentable utility. The use of the claimed uncharacterized polynucleotides in such studies would have provided no more information than the use of any other orphan polynucleotide. The asserted utility for the claimed polynucleotide is not specific to the claimed polynucleotide. Due to the lack of disclosure of a correlation between the claimed polynucleotides and a particular disorder, the asserted utility is also not substantial, as discussed above.

B. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is alleged as "well-established":

Beginning at p. 13 of the Brief, Appellant argues that the claimed polynucleotides are useful as tools for toxicology testing, drug discovery, and the diagnosis of disease and that these uses are "well-established". Each of these uses will be addressed individually, because the facts and issues directed to each use are distinct and separable. First, Appellant argues that toxicology testing is a well-established utility and concludes that the claimed polynucleotides could be used in this manner and that the claimed invention possesses utility. However, for a utility to be "well-established" it must be specific, substantial and credible. In this case, as indicated at page 13 of the Brief, all nucleic acids and genes are in some combination useful in toxicology testing.

However, the particulars of toxicology testing with the claimed polynucleotides are not disclosed in the instant specification. Neither the toxic substances nor the susceptible organ systems are identified. Therefore, this is a utility that would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to the claimed polynucleotides. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed polynucleotide in an array for toxicology screening is only useful in the sense that the information that is gained from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array. Again, this is a utility that would apply to virtually ever member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Appellant's individual polynucleotides are affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polynucleotides have no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information regarding this nucleic acid could be put.

With regard to drug discovery and development, Appellant mentions expression profiling as one use of the claimed polynucleotide. Appellant refers to recent developments as providing evidence that the benefits of this information are already beginning to manifest themselves. However, Appellant is incorrect in asserting that the efficacy (ability of producing a desired

effect) of a compound could be evaluated from the result of a transcript image because there is no way to assess the meaning of any individual hit obtained from this procedure. The first requirement is that one must know the biological significance of the polynucleotide(s) which is(are) being evaluated. Without this information, the results of the transcript image are useless because one would not know if the polynucleotide expression should be increased or decreased or even what significance could be attributed to such changes in expression profiles.

With regard to diagnosis of disease, in order for a polynucleotide to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polynucleotide and a disease or disorder. The presence of a polynucleotide in tissue that is derived from cancer cells is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed cDNA and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. overexpression). Evidence of a differential expression might serve as a basis for use of the claimed polynucleotides as diagnostics for diseases. However, in the absence of any disclosed relationship between the claimed polynucleotides or the proteins that are encoded thereby and any disease or disorder and the lack of any correlation between the claimed polynucleotides or the encoded proteins with any

known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

C. The similarity of the polypeptide encoded by the claimed invention to another polypeptide of undisputed utility is asserted to demonstrate utility

At p. 15 of the Brief, Appellant argues that the utility of the claimed polynucleotide can be imputed based on the relationship between MSP-9 and membrane spanning proteins. However, the Doerks reference was cited to show that it is commonly known in the art that sequence-to-function methods of assigning protein function are prone to errors. Doerks discusses several proteins that have had their function predicted based on homology to known proteins, for example, an assignment error was made for proteins gil2314657 and gil2688341 based on significant similarity to proline dipeptidases, when this assignment was based on similarity of a region that was not the active site (page 248 column 3, third full paragraph). The Brenner reference was cited to show that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Thus, based on the teachings of Doerks, Brenner and Bork, the determination of a function for an encoded polypeptide based on sequence data is difficult and does not provide a well-established utility for the claimed polypeptide and polynucleotide.

D. Objective evidence is alleged to corroborate the utilities of the claimed invention

Beginning at p. 17 of the Brief, Appellant argues that a "real-world" utility exists if actual use or commercial success can be shown. Citing case law, Appellant urges that such a showing is conclusive proof of utility. Appellant argues that a vibrant market has developed for databases containing all expressed genes, including those of Incyte, the real party at interest in the instant appeal. Appellant urges that Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven valuable, and that the databases including the claimed polynucleotide would be even more valuable. Appellant's arguments have been fully considered but are not deemed to be persuasive. The case law indicates that a rejection under 35 U.S.C. § 101 *for lack of operability* can be overcome by a showing of actual use or commercial success. The instant issue is whether or not the asserted utilities meet the three-pronged test for credibility, specificity, and substantiality. Such is not necessarily addressed by a showing of commercial success or actual use. As argued previously, many products that lack patentable utility enjoy commercial success, are actually used, and are considered valuable. These include silly fads such as pet rocks, but also include serious scientific products like orphan receptors.

III. The patent examiner's rejections are alleged as being without merit

A. The precise biological role or function of an expressed polynucleotide is alleged as being not required to demonstrate utility

Beginning at p. 17 of the Brief, Appellant characterizes the examiner's rejection as being based on the grounds that, without information as to the precise biological role of the claimed invention, the claimed invention lacks specific patentable utility. Appellant characterizes the

examiner's position as it is not enough that a person skilled in the art could use and would want to use the claimed invention either by itself or in a microarray, but that Appellant also is required to provide a specific and substantial interpretation of the results generated in a given expression analysis. Appellant argues that specific and substantial interpretations regarding biological function may be required by technical journals, but are not necessary for patents. Appellant urges that the relevant question is not how or why the invention works, but whether the invention provides an identifiable benefit. Appellant argues that the present invention meets this test. Appellant argues that the threshold for patentable utility is low. Appellant urges that only throwaway utilities are insufficient, and that knowledge of biological function is not required. This is not found to be persuasive, as it mischaracterizes the examiner's position. The rejection never states that the precise biological role of a polynucleotide is required for it to possess patentable utility. If a polynucleotide is disclosed as being differentially expressed in a disease or disorder, even if nothing is known or hypothesized about the activities of the encoded polypeptide, then the polynucleotide has patentable utility as a disease marker and in the toxicology/drug screening microarray assays discussed at length by Appellant. However, if a specification does not disclose such information, as is the case here, then there is no patentable utility. If a compound causes the claimed polynucleotide to be expressed at a decreased level in a microarray, does that mean the compound is a potential drug or a potential toxin? That determination requires significant further research, and thus the asserted utility is not substantial. Also, any expressed polynucleotide *can* be used in a microarray; thus the unasserted utility is also not specific.

B. Membership in a class of useful products can be proof of utility

Beginning at p. 19 of the Brief, Appellant asserts that the examiner improperly refused to impute the utility of the growth factor homolog family to the claimed invention. Appellant urges that the case law requires only that the class not contain a substantial number of useless members. Appellant urges that the examiner has treated the polynucleotide encoding MSP-9 as if it were in the general class of all polynucleotides, rather than the membrane spanning protein family. Appellant concludes that the examiner has not presented any evidence that the membrane spanning protein family class of proteins has any, let alone a substantial number, of useless members. This is not found to be persuasive. The membrane spanning protein family is functionally highly diverse, as evidenced by the references made of record in the rejection. When there is great functional diversity in a structurally related class of compounds, the class cannot be used to predict a utility for a new compound that fits in the class by structural similarity. Such is the case here.

Appellant argues that the membrane spanning protein family is known to involved in the transmission of signals across membranes, and the person of ordinary skill in the art need not know anything more about the claimed invention in order to be able to use it. Appellant urges that knowledge that MSP-9 is a membrane spanning protein is more than sufficient to make it useful. Appellant concludes that these facts must be accepted as true in the absence of evidence or sound scientific reasoning to the contrary. This is also not found to be persuasive. While it is true that some membrane spanning proteins are involved in cancer, immunological and reproductive disorders, there is a great diversity of cell types affected by these polypeptides. The specification does not disclose which cell types are responsive to the polypeptides encoded by

the claimed polynucleotides. Significant further research would be required of the skilled artisan to determine which cells are responsive, and thus the asserted utility is not substantial. Similarly, mere expression in a cancer cell does not mean that the polynucleotide is an appropriate target for drug development or toxicology testing. Cancer cells express many polynucleotides, such as constitutively expressed polynucleotides, which are not appropriate targets. The specification has not disclosed a specific disease or disorder of any type wherein the claimed polynucleotides are expressed at altered amounts or forms relative to the required control healthy tissue. Significant further research would be required of the skilled artisan to identify such a disease or disorder. Therefore the asserted utility is not substantial.

C. Because the uses of SEQ ID NO: 1-encoding and SEQ ID NO: 3-encoding polynucleotides in toxicology testing, drug discovery, and disease diagnosis are asserted as practical uses beyond mere study of the invention itself, the claimed invention is alleged to have utility.

At p. 20 of the Brief, Appellant argues that the rejection is incorrectly based on the grounds that the use of an invention as a tool for research is not a substantial use. Appellant urges that only a limited subset of research uses are not substantial: those in which the only known use for the claimed invention is to be an object of further study, thus merely inviting further research. This is not found to be persuasive. As discussed above, whereas a scale or a microarray or a gas chromatograph has patentable utility as a research tool, the objects being evaluated with those research tools do not necessarily have patentable utility. In the instant case, the claimed polynucleotide is not disclosed as having a specific activity, or having any property

(such as a differential pattern of expression in diseased tissue) that can be specifically useful. The claimed invention is, in fact, the object of further study, merely inviting further research. None of the utilities asserted for the claimed polynucleotide meets the test of being specific and substantial.

Beginning at p. 23 of the Brief, Appellant argues that the claims have been rejected based principally on citations to scientific literature identifying some of the difficulties in predicting protein function. Appellant urges that it is incorrect to question whether utility can be imputed to the claimed invention based on its homology to another polypeptide. Appellant characterizes the cited literature as not being inconsistent with Appellant's proof of homology by a reasonable probability. Appellant argues that the examiner has not made a showing that the assertion of utility cannot be accepted as true based on evidence that a person of ordinary skill would doubt the asserted utility by a reasonably probability. This is not found to be persuasive. Citations were also provided to references that specifically demonstrate that structural similarity in the growth factor and hormone family are not predictive of functional similarity. However, the Doerks reference was cited to show that it is commonly known in the art that sequence-to-function methods of assigning protein function are prone to errors. Doerks discusses several proteins that have had their function predicted based on homology to known proteins, for example, an assignment error was made for proteins gil2314657 and gil2688341 based on significant similarity to proline dipeptidases, when this assignment was based on similarity of a region that was not the active site (page 248 column 3, third full paragraph). The Brenner reference was cited to show that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature,

then most homologs must have different molecular and cellular functions. The Bork reference adds that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Thus, based on the teachings of Doerks, Brenner and Bork, the determination of a function for an encoded polypeptide based on sequence data is difficult and does not provide a well-established utility for the claimed polypeptide and polynucleotide. Based on this evidence, the person of ordinary skill in the art would reasonably doubt whether the polypeptides encoded by the claimed polynucleotides have functions similar to membrane spanning proteins.

IV. By requiring the patent Appellant to assert a particular or unique utility, it is alleged that the patent examination utility guidelines and training materials applied by the patent examiner misstate the law.

Beginning at page 25 of the Brief, Appellant challenges the legality of the Patent Examination Utility Guidelines. Since a Patent Examiner has no authority to comment on the legality of the Guidelines, this issue will be reserved for ruling by the Board of Patent Appeals and Interferences.

Issue 2: To the extent the rejection of the invention under 35 U.S.C. § 112, first paragraph, is based on the alleged improper rejection for lack of utility under 35 U.S.C. § 101, it is alleged that the rejection must be reversed

As Appellant indicates at page 27 of the Response, a rejection under § 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under § 101. *See, e.g., In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 2000); *In re Kirk*, 153 USPQ 48 (CCPA 1967).

Issue 3: It is alleged that the rejection under 35 USC § 112 first paragraph for lack of enablement is improper

The Brief at page 28 alleges that one of skill in the art would be able to isolate and identify variants of SEQ IOD NO: 26 which codes for variants of SEQ ID NO: 9 by screening the clones taught on page 29 of the Specification for variants in the polynucleotide sequences of each clone, and that such experimentation is considered routine when looking for mutations and genetic variability.

However, insufficient guidance is provided as to which of the myriad of variant nucleic acids encode polypeptides that will retain the characteristics of MSP-9. Appellants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible muteins of MSP-9. The Examiner has cited references that show that it is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. Since the claims encompass variant nucleic acids and polypeptides and given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to make and use the claimed invention,

especially since, as is the case here, the claims do not set forth a functional limitation for the polynucleotides are encoded polypeptides encompassed by the claims. Since the claims do not set forth a function for the polynucleotide or encoded polypeptide, and since the amino acid sequence of a polypeptide determines its structural and functional properties, and the predictability of which amino acids can be substituted is extremely complex and outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the polynucleotide and the encoded polypeptide are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. The claims encompass polynucleotides and polypeptides that the specification only teaches one skilled in the art to test for variants.

The Brief on page 29 also alleges that the specification teaches how to make the claimed polynucleotide variants using various methods such as direct synthesis and/or in combination with sequences from other proteins. However, it would require undue experimentation for one of skill in the art to make and use the claimed polynucleotides and encoded polypeptides, since the skilled artisan would have to first make polypeptide variants, but there is no functional limitation set forth for the claimed encoded polypeptides.

The Brief at page 30 further alleges that the Examiner has only provided an isolated example in which mutations can result in a change of the biological activity of a naturally occurring polypeptide. However, here Appellant has not provided a function which the claimed polynucleotide or encoded polypeptide must possess, thus one of skill in the art would need to

determine the function of the encoded polypeptide, then test for functional variants of the polynucleotide, which is beyond the realm of routine experimentation.

Issue 4: It is alleged that the rejection under 35 USC § 112 first paragraph for lack of written description is improper.

The Brief on page 32 alleges that the specification provides sufficient descriptive information, i.e. definitive structural features of the genus of polynucleotides and encoded polypeptides such that one of skill would be able to identify the claimed variants. However, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the Appellant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polynucleotides and encoded polypeptides. The claims do not meet the written description standard since, as is the case here, the claims do not set forth a functional limitation for the polynucleotides and encoded polypeptides encompassed by the claims. With the exception of SEQ ID NO: 26, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefore

conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. The Brief on page 33 alleges that given any naturally occurring polynucleotide sequence it would be routine for one of skill in the art to recognize whether it was a variant of SEQ ID NO: 26, and whether it encoded a variant of SEQ ID NO: 9. However, structural features that could distinguish the compounds in the genus from other seven transmembrane region compounds are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and polypeptides encompassed: there is no guidance in the art as to what the defining characteristics of the polypeptides might be since no functional limitation is set forth.

The Brief also alleges that the polynucleotides of the instant claims recite structural features, and the claims do not define a highly variant genus. However, while the claims encompass naturally occurring sequences, the specification fails to identify and describe regions essential to the function of the claimed invention, such as the untranslated regions, introns, and promoter sequences which are required since the invention encompasses naturally occurring sequences. Therefore, the structure of these elements is not conventional in the art and one of skill in the art would not recognize from the disclosure that Appellant was in possession of the genus of nucleic acids encompassed by the claimed invention.

Issue 5: It is alleged that the rejection of claim 7 under 35 USC § 112 first paragraph is improper.

The brief on page 38 alleges that one of skill in the art would know how to make and use the claimed transformed cells, based on the specification and the state of the art at the time the

application was filed, without undue experimentation because one of skill in the art would be able to make the claimed transformed cells in a culture and in vivo and use them to produce the claimed polypeptide. However, there are no actual or prophetic examples that disclose how to make or use host cells that comprise a DNA sequence as set forth in SEQ ID NO: 26 in an animal. The Examiner cites Eck & Wilson (page 81, column 2, second paragraph to page 82, column 1, second paragraph) who report that numerous factors complicate in vivo gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume distribution, rate of clearance into the tissues, etc.), the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. Since the instant disclosure does not address any of the methods necessary to make a host cell in an animal that comprises the polynucleotide of interest, the claim as written is not enabled.

Appellant argues that the claims do not need to be enabled for transfection of host cells in an animal, since the claims are enabled for host cells in culture, and that one of skill in the art would routinely be able to make a host cell in an animal. While the claims are enabled for a host cell in culture comprising the polynucleotide of SEQ ID NO: 26, the claims are not enabled for host cells within an animal that comprise the polynucleotide of SEQ IDNO: 26, it would require undue experimentation for one of skill in the art to detect which cells within the animal were transformed with the polynucleotide.

Issue 6: It is alleged that the rejection under 35 USC § 112 second paragraph is improper.

The Brief on page 42 alleges that the term "naturally occurring" is a limitation of the polynucleotide sequences comprised by the claimed polynucleotides and amino acids sequences, and that one of skill in the art would reasonably understand that the recitation of "naturally occurring" sequences encompasses any sequence which occurs in nature. However, in reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph "by providing clear warning to others as to what constitutes infringement of the patent". See, e.g., Solomon v. Kimberly-Clark Corp., 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000). MPEP 2173.02, MPEP 2173.02. In the instant case, the fact that Appellant argues that it is not a limitation on the encompassed polynucleotides and polypeptides, but that the use of the term imparts some information to one of skill in the art underscores the indefinite nature of the language. In the instant case, the claims are indefinite in the use of the term "naturally occurring" because the claim encompasses undiscovered sequences that occur in nature but are currently unknown. There would be no clear warning to others of a possible infringement since the possible infringer could not know whether the sequence at issue occurred in nature, thus the claims are indefinite.

Therefore, for reasons set forth above, Appellants arguments and exhibits have been fully and carefully considered, but are not considered sufficient to rebut the prima facie case of lack of utility and it is believed that the rejections should be sustained.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Joseph Murphy
May 17, 2004

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Conferees

Gary Kunz
SPE, Art Unit 1647

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Christina Chan
SPE, Art Unit 1644

INCYTE GENOMICS, INC.
3160 PORTER DRIVE
PALO ALTO, CA 94304